

REMARKS

Claims 1-8 and 11-19 are pending.

I. Claim Rejections Under 35 USC §102

The rejection of claims 1-3, 5-7, 11 and 12 under 35 U.S.C. 102(e) as being anticipated by Gorringer *et al.* (WO 01/73080 A2) is maintained for the reasons set forth in the previous office action.

Applicants traverse the rejection and its supporting remarks. Gorringer *et al.* fail to anticipate the pending claims since the Examiner has not cited to any single embodiment that encompasses all of the elements of the pending claims in their arrangement as claimed. In particular, claim 1 reads:

A process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and overexpresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

Thus, the TbpA must be overexpressed in *N. meningitidis* or *N. gonorrhoeae*, both of which are pathogenic or non-commensal strains, and outer membrane vesicles must be formed by membrane disruption in the absence of deoxycholate detergent. The Examiner has cited to the following portions of Gorringer *et al.*:

Page 4, lines 4, 5, and 12-14	Teaching expression of TbpA in organisms that express Tbps, but only citing obtaining outer membrane preparations from “commensal neisseria”
Page 5, lines 26-35	Again, teaching expression of TbpA in a “commensal Neisseria” or in <i>N. lactamica</i> – a non-pathogen or commensal host – and obtaining outer membrane vesicles from such.
Page 6, lines 1 and 2	Teaching extraction of TbpA using a non-ionic detergent.
Page 7, lines 16-20	Teaching where TbpA and other proteins may be derived

	<i>from</i> , i.e., where the gene for the protein was obtained – not where the proteins are expressed.
Page 12, lines 25-37 and page 13, lines 1-2	Teaching an embodiment of purification of TbpA expressed in <i>E. coli</i> .

Therefore, the Examiner has not cited to any teaching in Gorringer *et al.* regarding forming outer membrane vesicles from *N. meningitidis* or *N. gonorrhoeae* that overexpress TbpA. In fact, all of the sections cited by the Examiner that mention outer membrane vesicles teach that these outer membrane vesicles are generated using commensal strains of Neisseria. *N. meningitidis* and *N. gonorrhoeae* are pathogenic, i.e., non-commensal strains.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-7, 11 and 12.

II. Claim Rejections Under 35 USC §103

The rejection of claims 1-8, 11, 12 and 19 under 35 U.S.C. 103(a) as allegedly being unpatentable over Morein *et al.* (Analytical Biochemistry, 1994; 216: 47-51) in view of Gorringer *et al.* (WO 01/73080 A2) as applied to claims 1-3, 5-7, 11 and 12 above, and van der Ley *et al.* (Vaccine; 1995; 13(4): 401-407) and further in view of Rosenqvist *et al.* (WO 01/91788 A1) is maintained for the reasons set forth in the previous office action.

Applicants respectfully traverse the rejection and its supporting remarks. As discussed above, Gorringer *et al.* only teach overexpression of TbpA from pathogenic Neisseria in commensal Neisseria and generation of outer membrane vesicles from such bacteria. The Examiner has not identified any portion of Gorringer *et al.* or any other cited reference that teach overexpression of TbpA from pathogenic Neisseria in pathogenic Neisserial bacteria and generation of outer membrane vesicles from such bacteria. Thus, the obviousness rejection does not teach or suggest all of the claimed elements.

Furthermore, even if Gorringer *et al.* taught the claimed overexpression of TbpA in *N. meningitidis* or *N. gonorrhoeae* and subsequent outer membrane vesicles formation, neither Gorringer *et al.* nor Morein *et al.* teach formation of outer membrane vesicles from *N. meningitidis*

or *N. gonorrhoeae* without use of deoxycholate (claim 1) or any detergent (claim 2). The Examiner points to the extraction protocol on page 12 of Gorringer *et al.* for teaching formation of outer membrane vesicles without detergent. This extraction protocol is not relevant because it is part of a protocol for purifying recombinant TbpA to homogeneity (*i.e.*, an isolated protein, not a protein in an outer membrane vesicle) when expressed in *E. coli*. The bead beater was not used to form outer membrane vesicles from *N. meningitidis* or *N. gonorrhoeae*. The bead beater was used to disrupt membranes from *E. coli* after which the protein was purified. The Examiner has not provided any evidence why one of skill in the art would arbitrarily apply part of a protein purification protocol to generate outer membrane vesicle from an entirely unrelated bacteria. Similarly, Morein *et al.* does not teach a method of forming outer membrane vesicles from *N. meningitidis* or *N. gonorrhoeae*. Morein *et al.* teach how to separate inner and outer membrane vesicles from *E. coli*. Again, the Examiner has not provided any evidence that one of skill in the art would use a technique from *E. coli* on *N. meningitidis* or *N. gonorrhoeae*.

In fact, Rosenqvist *et al.* actually provide express reasons to use deoxycholate to form outer membrane vesicles from *N. meningitidis* or *N. gonorrhoeae* due to unique characteristics of their membrane. On page 7, lines 6-17, Rosenqvist *et al.* teach that deoxycholate is used to extract outer membrane vesicles from *N. meningitidis* for a number of reasons: deoxycholate is effective at killing the bacteria (necessary for a pathogenic bacteria, but not for a commensal bacteria); deoxycholate is effective at breaking up the outer membrane to form outer membrane vesicles while retaining the outer membrane proteins in their native state, and most importantly, “dissolving and releasing most of the toxic lipopolysaccharides from the outer membrane, and also making the LPS remaining in the vaccine less toxic.” Thus, there is affirmative evidence on the record that one of skill in the art would not arbitrarily apply techniques to generate outer membrane vesicles from other bacteria to *N. meningitidis* or *N. gonorrhoeae* due to these pathogenic bacteria having toxic lipopolysaccharides in their membrane and the need to completely kill pathogenic bacteria.

Finally, it is worth noting that the Examiner had previously rejected the pending claims as obvious over Robinson *et al.* (U.S. Pat. No. 7,081,244), which disclosed expression of Tbps in

commensal Neisserial strains. The Examiner withdrew the rejection after the Applicant argued that the proposed modification of Robinson *et al.* to replace the commensal Neisserial strains with pathogenic Neisserial strains such as *N. meningitidis* or *N. gonorrhoeae* would render Robinson's invention unsuitable for its intended purpose due to Robinson expressly teaching the problems associated with use of *N. meningitidis* or *N. gonorrhoeae* and the advantages of commensal Neisserial strains. The Examiner appears to have merely replaced Robinson *et al.* with Gorringer *et al.*, which both teach expression of Tbps in commensal Neisserial strains to make outer membrane vesicles, because Gorringer *et al.* does not express the rationale behind the choice of commensal strains while Robinson *et al.* does. Gorringer *et al.* certainly chose commensal strains for the same reasons that Robinson *et al.* did, *e.g.*, lack of bacterial toxins (such as LPS), greater safety due to being a non-pathogenic strain, *etc.* Thus, one of skill in the art would not be motivated to modify Gorringer *et al.* any more than Robinson *et al.*

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-7, 11 and 12.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002100800**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 6, 2010

Respectfully submitted,

By /Otis Littlefield/

Otis B. Littlefield

Registration No.: 48,751

MORRISON & FOERSTER LLP

425 Market Street

San Francisco, California 94105-2482

Telephone: 415.268.6846

Fax: 415.268.7522